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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,307	07/22/2004	Roberto Burioni	937-PCT-US	9195

7590 03/02/2007

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EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	PAPER NUMBER
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,307	BURIONI, ROBERTO	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3, 12-29* is/are pending in the application.

4a) Of the above claim(s) *12-26 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/22 8/20 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-3 and 12-29 are pending in the application.

Election/Restrictions

2. Applicant's election with traverse of Group I, and the species of claim 2, in the reply filed on February 14, 2007 is acknowledged. The traversal is on the ground(s) that the Examiner has not shown that the two requirements of U.S. restriction practice (distinctness and burden) have not been shown. This is not found persuasive because, the present application is a 371 application (i.e. a national stage of an international application under the PCT). As such, U.S. restriction does not apply to the present claims. Rather, PCT unity of invention is the appropriate means by which restriction is determined in the present application. See, MPEP § 1893.03(d). As was shown in the restriction requirement, there is no unity of invention among the claimed inventions. The Applicant's arguments in traversal are therefore not found persuasive.

The requirement is still deemed proper and is therefore made FINAL.

However, it was determined that a search for the additional antibody of claim 3 was not unduly burdensome. The species election between the antibodies of claims 2 and 3 is therefore withdrawn.

3. Claims 12-26, and 29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on February 14, 2007.

4. Claims 1, 2, 27, and 28 are under consideration.

Information Disclosure Statement

5. The information disclosure statements (IDS) submitted on July 20 and August 22, 2004 in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Sequence Listing

6. The specification, and claims 2 and 3, are objected to for containing referring to sequences without also identifying them by the sequence identifier assigned to them in the sequence listing as required by 37 CFR 1.821(d). See, pages. 3, 4, and 8-12. See also, claim 2. The examiner would like to bring the applicant's attention to the following excerpt from MPEP §2422.03:

> 37 CFR 1.821(d) requires the use of the assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences regardless of whether a given sequence is also embedded in the text of the description or claims of an application. This requirement is also intended to permit references, in both the description and claims, to sequences set forth in the "Sequence Listing" by the use of assigned sequence identifiers without repeating the sequence in the text of the description or claims. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented sequence. For example, language such as "residues 14 to 243 of SEQ ID NO:23" is permissible and the fragment need not be separately presented in the "Sequence Listing." Where a sequence is embedded in the text of an application, it must be presented in a manner that complies with the requirements of the sequence rules.

The applicant is therefore required to amend the specification to comply with 37 CFR 1.821(d).

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1, 27, and 28 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. These claims are drawn to compositions comprising a human antibody that binds to the HCV E2 protein and that has in vivo neutralizing activity. The claim therefore reads on compositions found in nature. For example, Schofield teaches that such neutralizing antibodies may be found in serum samples from persons infected with HCV. Thus, the reference demonstrates that the antibodies and compositions of the claims read on antibodies and compositions found in nature. It is suggested that the claims be amended to read on isolated or purified antibodies.

Claim Rejections - 35 USC § 112

9. Claims 1-3, 27, and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 reads on a human antibody, or fragment thereof. Such a claim would be read to mean an antibody produced by a human, or on functional fragments comprising the variable regions thereof. However, claim 2 further describes the antibody as being the antibody of e137. It is first noted that the e137 molecule disclosed in the application is not an antibody, but is a Fab antibody fragment. Thus, it is not clear if claim 2 is being drawn to an antibody comprising the variable domains of SEQ ID NOs: 7 and 8 (representing the antibody heavy and light chains respectively), or if the claim is being drawn to the e137 Fab fragment.

Claim 3 provides similar teachings to claim 2 (albeit based on a different Fab fragment), and therefore suffers similar indefiniteness.

Moreover, the application also teaches that the e137 and e301 Fabs were derived not from an antibody produced from a human, but according to the method of Burioni et al., Hepatology 28:810-14. This reference teaches that these fragments were artificially created as part of a random combinatorial phage library. Pages 810-811. In view of this indication that the indicated variable sequences are not of human origin, the fact that the claims are drawn to a "human antibody," and the identification in claims 2 and 3 of the e137 and e301 "antibodies" as "human antibodies," it is not clear what is meant by the term "human antibody." Because the application indicates that non-human antibodies fall within the scope of the term "human antibody," it is not clear from the application or the claims what the meets and bounds of the claims are.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 27 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions for inhibiting HCV E2 binding to a cell (i.e. having neutralizing activity), does not reasonably provide enablement for compositions for anti-HCV therapy comprising such neutralizing antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. Those factors considered most relevant in the present application are the nature of the invention, the sate of the prior art, and the breadth of the claims.

The rejected claim is drawn to a composition effective for the therapy of HCV infections. In support of the claimed invention, the application demonstrates in vitro inhibition of HCV E2 binding to a cell using the claimed antibodies. However, it is noted that the present application also provides teachings demonstrating that the neutralizing activity of an anti-HCV antibody does not correlate to its ability to inhibit HCV infection. For example, the application teaches that the most effective antibody fragment (e509) for inhibiting E2 binding to a cell receptor actually resulted in the enhancement of infection of a cell by a pseudotype virus. (page 17, Table 2). The same teachings also demonstrate that two Fab antibody fragments with the same ability to inhibit E2/receptor binding had different effects on infection by the pseudotypes virus- with one Fab (e20) having no effect, and the other (e301) having a strong inhibitory effect. These teachings also show that the e137 Fab, which is disclosed as having low binding inhibition, resulted in the a strong inhibition of pseudotype virus infection. These teachings demonstrate

significant unpredictability in the ability of any particular neutralizing antibody (or fragment) to provide a therapeutic effect on viral infection. This is because the in vitro E2 neutralization activity does not appear to correlate to the ability of a given antibody to inhibit viral infection.

Further, the teachings in the art of treating HCV infections also indicate that there is significant unpredictability in the use of the claimed compositions for the treatment of HCV infection. It is noted that the art teaches that the development of anti-HCV therapeutics has been hampered by several difficulties. See e.g., Bretner, Acta Biochim Pol 52:57-70 at 58; and Leroux-Roels, Expert Rev Vaccines 4:351-71, at 356. The art indicates that, to date, the only effective therapy (for about 50% of the patients) is administration of interferon and ribavirin. Leroux-Roels, page 352. No immunotherapeutic methods have been shown to be effective. The art therefore indicates that the art of anti-HCV immunotherapy, passive or otherwise, is not yet established. This is despite the previously development of neutralizing anti-HCV E2 antibodies. See e.g., Burioni et al. (Hepatology 28:810-14); and Habersetzer et al. (Virology 249: 32-41). Thus, the art both indicates that the field of developing anti-HCV therapeutics, including passive antibody therapies, is relatively undeveloped, and that the development of such therapeutics faces significant challenges (i.e., is unpredictable).

In view of these teachings in the prior art, the lack of any indication of in vivo therapeutic efficacy, and the teachings in the application demonstrating disparate effects on viral infection by different anti-E2 neutralizing antibodies, the claim is rejected as exceeding the scope for which an enabling disclosure has been provided.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1, 27, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Burioni et al. (Hepatology 28:810-14). These claims are drawn to an antibody composition comprising a neutralizing anti-HCV E2 antibody or functional fragments thereof.

Burioni teaches a number of anti-HCV neutralizing antibody Fab fragments, including the e137 antibody. Page 811, and page 812 (esp., Fig 1). The reference further teaches compositions of the purified Fab fragments, which compositions could be used as indicated in claim 28. Moreover, because the reference discloses the same antibody as identified by the present claims, the reference would inherently meet the additional functional limitations of this antibody as required by claims 27 and 28. The reference therefore anticipates the indicated claims.

14. Claims 1, 27, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Habersetzer et al. (Virology 249: 32-41- of record in the action mailed on August 23, 2006). These claims have been described above. An anti-HCV E2 neutralizing human MAb is disclosed by Habersetzer. See e.g., page 36, right column. The reference therefor anticipates the indicated claims.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 1-3, 27, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burioni as applied to claims 1, 27, and 28, further in view of the teachings of Poul et al. (Immunotechnology 1: 189-96) and Foung et al. (U.S. 7,091,324). Claims 1, 27, and 28 have been described above. Claim 2 is further limited to such an antibody comprising, respectively, the heavy chain and light chain sequences of SEQ ID NOs: 7 and 8 (disclosed as the e137 antibody on pages 8-9 of the application). Claim 3 reads on the antibody wherein it comprises the variable sequences of SEQ ID NOs: 9 and 10. For the purposes of this rejection, claims 2 and 3 are read as describing on any full-length antibody comprising the indicated variable domains and human antibody constant regions.

As indicated above, Burioni teaches the production of a series of neutralizing anti-HCV E2 antibody Fab fragments. Among the Fab fragments disclosed by the reference are the e137 and e301 Fabs, and the sequences of their heavy and light chain variable domains. Page 811, and page 812 (esp., Fig 1). The reference also suggests the use of such antibody fragments for the study of anti-HCV immune response. However, while the reference teaches the Fab fragments, the reference does not teach a full-length human antibody comprising these variable domain sequences.

Nonetheless, it is recognized in the art that full-length antibodies and Fab fragments are considered to be functional equivalents for antigen binding purposes. See e.g., Foung et al., U.S.

7,091,324, column 5. It is noted that the Foung reference also teaches the use of human monoclonal antibodies for the study of the anti-HCV immune response. Additionally, the Poul teaches that it was also known in the art to construct full-length human antibodies from variable domains identified from combinatorial libraries (such as in Burioni). See e.g., abstract, and page 195 (last text paragraph). Thus, it would have been obvious to those of ordinary skill in the art to make full-length humanized antibodies comprising the variable domains of the e137 and e301Fabs as a functional equivalent for the Fab fragments identified in Burioni. The combined teachings of these references therefore render the claimed inventions obvious.

Conclusion

17. No claims are allowed.

18. The following prior art references are made of record and considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

> Foung et al., U.S. 7,091,324. This reference teaches neutralizing anti-HCV E2 antibodies. The reference is considered redundant to the Habersetzer and Burioni references applied above. .

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Z. Lucas
Patent Examiner